A New Synthetic Route to *P*-Chiral Phosphine-Boranes of High Enantiopurity via Stereocontrolled Pd(0)−Cu(I) Cocatalyzed Aromatic Phosphorylation

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Enantiopure phosphine-boranes have come to be recognized as the precursors of choice for the synthesis of a wide variety of diphosphine ligands which are used for asymmetric catalysis.[1] The methods which have been most frequently employed for the synthesis of enantioenriched phosphine-boranes involve the formation of phosphorus−carbon bonds via successive nucleophilic displacements at phosphorus.[2,3] Nucleophilic substitution at tetracoordinate phosphorus typically proceeds via pentacoordinate intermediates in which stereochemical leakage can occur via pseudorotation.[4] Consequently, the utilization of this type of approach for the synthesis of an extensive series of structurally varied phosphine-boranes in high optical purity has not been realized. In principle, *electrophilic* arylation of enantiomerically pure secondary phosphine-boranes would provide a means by which degradation of phosphorus stereointegrity via pseudorotation could be avoided. In this communication we show that (S_p)-methylphenylphosphine-borane (**1**) undergoes Pd(0)−Cu(I) cocatalyzed cross-coupling[5] with aryl iodides with excellent levels of absolute stereocontrol.

Imamoto and Oshiki reported that both diastereomers of menthyl phenylphosphinite-borane are capable of taking part in palladium-catalyzed cross-coupling with 2-iodoanisole with essentially complete retention or inversion of configuration at phosphorus as a function of solvent polarity.[6,7] We began our investigation by examining the Pd(0) mediated cross-coupling of (S_p)-methylphenylphosphine-borane (**1**)[8] with 2-iodotoluene. Unfortunately, initial efforts to achieve this transformation under the various sets of reaction conditions described previously[6] gave unsatisfactory results in that partial loss of stereochemical integrity or modest yields of the desired product (**3a**) were obtained. In all likelihood, the propensity of secondary phosphine-borane anions to undergo pyramidal inversion[9,10] was responsible for the erosion of stereocontrol in these instances. It was our expectation that base-mediated racemization of the putative anionic intermediate could be effectively suppressed by rapid complexation with an appropriate cation to generate a configurationally stable metallophosphide (Scheme 1). In accord with this hypothesis, the addition of sub-stoichiometric quantities (10−30 mol %) of CuI[13] was found to increase the efficiency and stereocontrol associated with Pd(0) catalyzed aromatic phosphorylation. It is of additional significance that representative cross-couplings were found to proceed at temperatures of −10 °C to 0 °C in the presence of CuI.[14,15] After considerable experimentation, the conversion of **1** to **3a** could optimally be achieved by treatment with 2-iodotoluene (1.5 equiv) in the presence of preformed "Pd-[P(Me)Ph_2]$_2$"[16] (7.5 mol %), CuI (20−30 mol %) and (*i*-Pr)$_2$NEt (1.2 equiv) in THF−Me_2S (4:1) at 0 °C.

A variety of alternative supporting ligands [including tris(2-furyl)phosphine and Ph_3As][17] and solvent systems were evaluated and found to be inferior in representative cross-coupling reactions. Specifically, the use of less polar solvents (e.g., $PhCH_3$ and Et_2O) led to suppression of reaction rates whereas more polar media [DMF, *N*-methylpyrrolidinone or THF−HMPA (9:1)] provided excellent rates of substrate conversion but with lower overall efficiency and reduced stereoselectivity. In accordance with our initial expectations, reaction of (S_p) **1** with 2-iodotoluene resulted in *retention* of configuration

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(6) Oshiki, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975.

(7) For examples involving the Pd(0) catalyzed cross-coupling of enantioenriched isopropyl arylmethyl phosphinates see: (a) Zhang, J.; Xu, Y. *J. Chem. Soc. Chem. Commun.* **1986**, 1606. (b) Zhang, J.; Xu, Y.; Huang, G.; Guo, H. *Tetrahedron Lett.* **1988**, *29*, 1955. (c) Xu, Y.; Wei, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949.

(8) (a) The synthesis of **1** (optical purity >99%)[8b] was achieved by the method of Imamoto involving the reduction of (menthyloxy)-methylphenylphosphine-borane with lithium naphthalenide.[9] b) The optical purity of **1** was established by conversion to the *P*-benzyl derivative [(a) *n*-BuLi, −78 °C; (b) BnBr] followed by HPLC analysis.[18]

(9) Oshiki, T.; Hikosaka, T.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32*, 3371.

(10) Base-mediated *P*-benzylation of **1** under conditions which led to the stereospecific alkylation (retention) of (S_p)-menthyl phenylphosphinite−borane[11] results in complete racemization: Kumaraswamy, G.; Livinghouse, T., unpublished observations.

(11) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.

(12) Oshiki, T.; Imamoto, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3719.

(13) The presence of sub-stoichiometric quantities of CuI has been shown to increase the efficiency of certain Stille-type cross coupling reactions as well as Castro-Stevens alkynylations: (a) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408. (b) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997. (c) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600. (d) Additional related work has been reported by Piers: Piers, E.; Romaro, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215.

(14) Representative cross-couplings that were conducted at higher temperatures (e.g., 25 °C) resulted in lower product ee's.

(15) Phosphine-borane **1** was found to undergo relatively rapid racemization in the presence of Et_3N in THF solution at 25 °C. Significantly, Et_3N-mediated racemization of **1** was shown to be a comparatively slow process at 0 °C.

(16) Prepared in-situ by treating $Pd(OAc)_2$ with $Me(Ph)_2P$ (3 equiv) in THF: Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195.

(17) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

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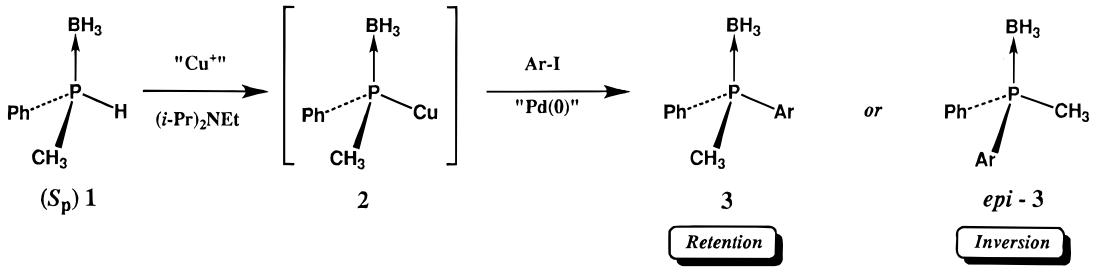
Scheme 1



at phosphorus to provide (R_p) **3a** with excellent stereoselectivity.[19] It is also of interest that the polarity of the reaction medium had very little influence on the absolute stereochemical outcome of substitution when CuI was present. The latter result contrasts with the findings of Imamoto involving menthyl phenylphosphinite−borane in the absence of CuI.[6] Although $(Ph_3P)_4Pd$ was found an effective catalyst, superior results and enhanced reproducibility were obtained with catalysts generated in-situ from $Pd(OAc)_2 + 3\ R_3P$.[16] In this connection it is noteworthy that highly electron-rich phosphines [e.g., n-Bu_3P, $(n\text{-Bu})_2PhP$, $(i\text{-Pr})_2PhP$ and $(Cy)_3P$] gave relatively ineffective Pd(0) catalyst systems when compared to the catalyst generated from $Me(Ph)_2P$. A series of representative cross-coupling reactions was subsequently conducted employing **1**[8] and various aryl iodides. The results of this study are shown in Table 1.

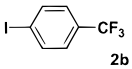
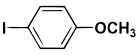
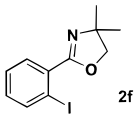
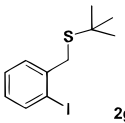
Several features of the above results are worthy of comment. Excellent levels of stereocontrol are maintained over a rather wide range of sterically differentiated reaction components.[18] In this regard it is preparatively significant that the overall yields and ee's obtained via Pd(0)−Cu(I) cross-coupling exceed those achievable by direct nucleophilic alkoxide displacement.[2b,12,19] In addition, representative arene phosphorylations can readily be carried out on a preparative scale.

In summary, we have shown that Pd(0)−Cu(I) cocatalyzed aromatic phosphorylation is an excellent method for the synthesis of phosphine-boranes in a very high state of optical purity. The scope of this reaction is currently being extended to the synthesis of new bidentate ligand domains for asymmetric catalysis.

Experimental Section

General Methods. All experiments were carried out under an argon atmosphere in oven-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl. Methyldiphenylphosphine and palladium(II) acetate were purchased from Strem Chemicals, Inc., and copper(I) iodide was purified by precipitation from aqueous KI. All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Column flash chromatography was performed on Merck silica gel 60 (230−400 mesh) and Aldrich neutral alumina (~150 mesh). Chiral HPLC was performed using a chiralpak AD [250 × 4.6 mm (L X I. D.)] HPLC column (Daicel Chemical Industries).

Table 1

Entry	(Sp) 1	Ar-I 2	3	%yield[a]	%ee[b]
1	1	 2a	3a	75	>99
2	1	 2b	3b	65	>99
3	1	 2c	3c	98	98.5(>99)[c]
4	1	 2d	3d	75	94.5
5	1	 2e	3e	52	97.7
6	1	 2f	3f	68	>99
7	1	 2g	3g	62	>99

[a] Isolated yield. [b] All ee's were determined by HPLC chromatography using a chiralpak AD HPLC column. [c] After recrystallization from hexane/2-propanol.

General Procedure for Stereocontrolled Arene Phosphorylation. (*R*)-(2-Methylphenyl)phenylmethylphosphine-borane (3a). To a solution of $Pd(OAc)_2$ (7.5 mol %, 8.5 mg) in dry THF (0.5 mL) under an argon atmosphere was added diphenylmethylphosphine (22 mol %, 0.022 mL) and the resulting mixture was allowed to stir for 10 min at room temperature. 2-Iodotoluene (**2a**) (1.5 equiv, 0.09 mL) was then added and stirring was continued at room temperature. In another flask, CuI (30 mol %, 30 mg) was dissolved in a mixture of THF (0.25 mL) and Me_2S (0.2 mL) under argon and then $(i\text{-Pr})_2NEt$ (1.2 equiv, 0.1 mL) and (*S*p)-Methylphenylphosphine-borane **1** (0.5 mmol, 0.078 mL) were sequentially added at 0 °C. The solution of the palladium complex was then added to the phosphine-borane solution by cannula and the resulting mixture was stirred for 3 days at 0 °C. The reaction mixture was quenched by the addition of water, extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the crude product was subjected to silica gel chromatography using hexane followed by hexane/CH_2Cl_2 (5/1). The pure product **3a** was isolated as a colorless liquid (85 mg, 75%) (entry 1). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.73−7.14 (m, 9H, $-C_6H_5$, $-C_6H_4-$), 2.17 (s, 3H, CH_3), 1.85 (d, J = 9.9 Hz, 3H, $-CH_3$), 1.54−0.48 (br m, 3H, BH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 142.8, 132.8, 131.9, 129.3, 126.5, 22.1, 13.6. ^{31}P NMR

(18) Enantiomeric purity was established by HPLC using a Chiralpak AD HPLC column.

(19) An authentic specimen of phosphine-borane **3a** was prepared by the procedure of Juge[2b] for comparative purposes and shown to possess a configuration *identical*[18] to that synthesized via Pd(0)−Cu(I) cocatalyzed cross-coupling. It is also of significance that the sample of **3a** prepared in this manner was obtained in lower enantiomeric purity and yield when compared to the present cross-coupling procedure.

($CDCl_3$, 121 MHz): δ 10.76. HRMS: calcd for $C_{14}H_{15}P$ ($M^+ - BH_3$) 214.0913, found 214.0911. $[\alpha]^{25}_D = -27°$ ($c = 1.0$, CH_3OH). Separation of enantiomers by chiral HPLC (Daicel Chiral Pak AD column, flow rate 1 mL/min, 99% hexane, 1% 2-propanol, Tr 11.79, 12.66 min) determined the ee to be >99%.

In case of compound **3f** and **3g** the crude products were subjected to purification by chromatography on neutral alumina. Cross-coupling reactions performed using 5.0 mmol of starting phosphine-borane provide arylation products in comparable yields and enantiopurity.

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Supporting Information Available: Spectral data for compounds **3b**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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